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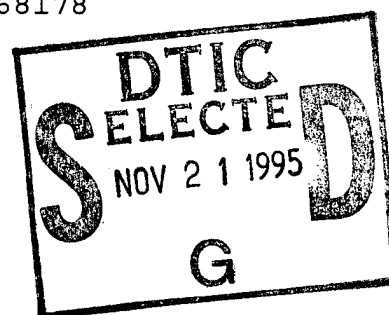
TITLE: Genetic Counseling Using BRCA-1-Linked Markers

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REPORT DATE: September 1995

TYPE OF REPORT: Annual



PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE

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1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE September 1995	3. REPORT TYPE AND DATES COVERED Annual 1 Sep 94 - 31 Aug 95	
4. TITLE AND SUBTITLE Genetic Counseling Using BRCA-1-Linked Markers			5. FUNDING NUMBERS DAMD17-94-J-4340	
6. AUTHOR(S) Dr. Henry T. Lynch				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Creighton University Omaha, Nebraska 68178			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION STATEMENT	
ABSTRACT (Maximum 200 words) <i>Advances in molecular genetics have made it possible to identify individuals who have a strong inherited predisposition to breast cancer ovarian cancer. Because experience in genetic counseling of members of hereditary breast cancer families is exceedingly limited, we have mounted a study focusing on the genetic counseling process, with particular attention to the psychological impact and to adherence to recommended surveillance. To date, we have provided genetic counseling to 249 individuals from eight hereditary breast/ovarian cancer families. Of the 249 participants in the baseline (pre-counseling) telephone interviews (response rate to interviews - 77%), 75% of respondents opted to receive their BRCA1 test results. Using logistic regression analysis, we identified the following positive predictors of acceptance of testing: female gender (OR=5.0; CI=1.2-20.9), higher education level (OR=9.2; CI=1.2-70.7), and high baseline distress level (OR=7.8; CI=2.0-30.8). We observed significant improvement in knowledge from baseline to one-month follow-up for both carriers and non-carriers (F (time) = 47.2; $p=.0001$). By one month following counseling, female mutation carriers showed an increase in breast cancer worries, while non-carriers showed a decrease (F (time by group) = 4.6; $p=.02$). By six months, carriers had significantly higher scores on a depression measure ($F=2.1$; $p=.04$). We continue to accrue additional families and to evaluate the short- and long-term impact of BRCA1 testing.</i>				
13. SUBJECT TERMS Hereditary breast cancer, BRCA1, genetic counseling			15. NUMBER OF PAGES 37	
			16. PRICE CODE	
14. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

1-101-280-5500

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FOREWORD

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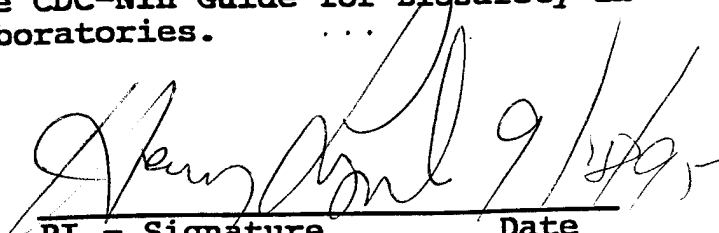
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INTRODUCTION:

Advances in the molecular genetics of hereditary breast cancer have provided the heretofore unprecedented opportunity for DNA-based genetic counseling. This now enables physicians, in concert with certified genetic counselors, to delicately provide family members with information pertinent to whether or not they have inherited a cancer predisposing gene, and in our case this has involved BRCA1 and, ultimately will involve BRCA2 and p53.

These unheralded opportunities followed the work of Hall, et al. Hall et al. [1] who identified linkage of breast cancer susceptibility to the D17S74 locus (probe CMM86) on chromosome 17q21. Shortly after, linkage to D17S74 was confirmed in three of five families with hereditary breast/ovarian cancer (HBOC)[2]. An international consortium studying linkage to hereditary breast/ovarian cancer reported that 45% of site-specific breast cancer families [3] and 92% of families with HBOC syndrome were linked to BRCA1 [4]. However, none of the families with male breast cancer were linked to BRCA1. There is an increased risk for cancer of the colon and prostate in BRCA1 carriers.

A second gene, BRCA2, was mapped to chromosome 13 in 1994 [5]. The majority of families with cases of male breast cancer appear to be associated with BRCA2. BRCA2 confers a high risk of breast cancer, but not, it seems, for ovarian cancer. More research is needed with respect to the full tumor spectrum in BRCA1 and 2.

Easton et al. [6] estimate the frequency of BRCA1 mutant alleles to be 0.0007, based on 44 breast cancer deaths occurring among the relatives of 1203 women with ovarian cancer (31.8 expected). It is therefore likely that the frequency of carriers of BRCA1 mutations in the population is closer to one in 500. Ford et al. [7] estimate a cumulative risk of 48% to age 70 for ovarian cancer and 85% for breast cancer. However the data best fit a model with a mix of two susceptibility genes; one with a risk for breast cancer of 71% and for ovarian cancer of 87% to age 70 and a second gene with a risk for breast cancer of 86% to age 70 and a risk for ovarian cancer of only 18%. Little linkage data are available for apparent site-specific ovarian cancer, but a few rare families have been linked to BRCA1 [8].

Based on limited data, it appears that mutations can be identified in the coding region of the BRCA1 gene in over one-half of HBOC syndrome families. It is likely that mutations in the splice junctions, introns and regulatory regions of BRCA1 are responsible for most of the other families, but a small proportion will be unlinked. With this knowledge, it is now feasible to offer predictive testing based on BRCA1 gene analysis to women from HBC or HBOC families. Because of scientific, psychological, and social concerns, predictive testing programs are currently restricted to specialized research centers.

Lerman et al have conducted extensive research on the psychological

impact of cancer risk notification and adherence to cancer screening. She and her colleagues demonstrated that cancer risk notification can produce negative psychological consequences, including anxiety, traumatic stress symptoms, and impairment in daily functioning [9,10], and that distress can impair adherence to recommended surveillance [11-13]. While most of her work has focused on breast cancer, she has collaborated on studies of colon cancer risk and screening [11,14-16]. Her more recent work focuses on psychological issues in genetic testing for cancer susceptibility [17,18], including a recent study which showed that anxiety can interfere with comprehension of genetic risk information [19].

Goals and Objectives

The goals of our study are to identify the impact of genetic counseling in HBC and HBOC families where gene linkage to BRCA1 has been identified. This study is designed to demonstrate the feasibility of genetic counseling for HBC and HBOC, and to evaluate the impact of counseling on psychological state and medical behavior. The subject of genetic counseling in HBC and HBOC has never been systematically investigated in either a research or clinical setting. The study is also designed to examine predictors of those adverse consequences that could evolve from this genetic counseling. This information may enable physicians and genetic counselors to anticipate and prevent problems in individual clients.

BODY:

Eligible members of BRCA1-linked families receive an introductory letter, followed by a baseline, structured telephone interview administered by a trained interviewer at Georgetown University under the direction of Caryn Lerman Ph.D., a clinical psychologist/geneticist at Georgetown University, Washington, D.C.. About four weeks later, these individuals have an opportunity to attend an education session at which time information about gene linkage, hereditary breast cancer and surveillance measures are again reinforced prior to individual counseling to obtain genetic test results for breast-ovarian cancer susceptibility.

All genetic counseling and testing is provided by, and/or supervised by Dr. Lynch and his colleagues. Telephone interviews are conducted from Georgetown University at one-, six-, twelve-, and twenty-four months following genetic counseling to evaluate the impact of disclosure of genetic information.

Progress in our study of genetic counseling based on BRCA1 linked markers has been extremely well-targeted and productive. We have collected 319 blood specimens for DNA analysis from a total of 43 families. The DNA is used in the search for germline mutations, in collaboration with Steven Narod, M.D., of McGill University in Montreal, Canada, and Gilbert Lenoir, Ph.D., D.V.N., in Lyon, France.

To date, genetic counseling has been provided to eight HBOC families where BRCA1 germline mutations have been identified. Pedigrees of these eight families are shown in Figures 1-8 (see Appendix). The Table shows the family number, the date when the family was counseled, and the number of members who were counseled and provided with individual risk assessment in each of the eight families. The 43 well-defined HBC/HBOC families in our resource which have sufficient gene linkage and/or DNA mutation information available are eligible for counseling in the future. The most informative of these families are being set up with appointments for genetic counseling.

TABLE

Family Number	Date Family was Counseled	Number of Members Counseled
1234	August 20, 1994	21
1813	January 29, 1995	9
1816	August 19, 1995	16
1973	May 27, 1995	12
2090	February 18, 1995	10
2651	April 22, 1995	29
2770	March 18, 1995	32
3079	June 10, 1995	9

Individuals counseled since August 1, 1994 and the date on which they were counseled.

Since this grant was awarded we have identified 76 new breast cancer prone families. Of these, by pedigree analysis, 29 have

been diagnosed as consistent with HBC and 16 with the HBOC syndrome. Pedigrees of these families have been sent to Steven Narod, M.D. to determine eligibility for linkage analysis.

To date, a total of 249 individuals have participated in the baseline (pre-counseling) telephone interviews (response rate to interviews -77%). In terms of their demographic backgrounds, 100% of respondents are white, 69% are female, 88% have a high school education or greater, and 71% are employed. The average age of respondents is 43 +/- 14 years.

Thus far, about 75% of respondents have opted to receive their BRCA1 test results and 25% have declined. We conducted logistic regression analysis to identify predictors of acceptance of testing. Significant positive predictors include: female gender (OR=5.0; CI=1.2-20.9), higher education level (OR=9.2; CI=1.2-70.7), and high baseline distress level (OR=7.8; CI=2.0-30.8). Other factors have significant bivariate associations with uptake of testing include having health insurance and being more knowledgeable about hereditary breast cancer.

We have also conducted preliminary analyses of the impact of BRCA1 testing on psychological outcomes. Our data show significant improvements in knowledge from baseline to one-month follow-up for both carriers and noncarriers (F (time) =47.2; $p=.0001$). By one-month following counseling, female

mutation carriers showed an increase in breast cancer worries, while noncarriers showed a decrease (F (time by group)=4.6; p =.02). There were no significant differences between carriers and noncarriers in depression at one-month follow-up. However, by six months, carriers had significantly higher scores on a depression measure (F =2.1; p =.04). Increases in depression in the mutation carriers was predicted by specific coping strategies involving venting of feelings, information-seeking, and planful problem-solving.

CONCLUSIONS:

These preliminary data provide support for the feasibility of our ongoing research and the potential to elucidate clinically important information. However, since only a subset of the sample have been enrolled to date, it may be premature to draw conclusions from these data. Nonetheless, the following tentative interpretations may be made: (1) individuals who present for genetic testing are more likely to be female and to be more distressed about their risk. This points to the need to address patients' psychosocial concerns during the genetic counseling visit; (2) any adverse effects of genetic counseling may not be obvious in the short term. This underscores the need for long-term follow-up of participants in genetic counseling programs; (3) in the short term, coping strategies involving acceptance may be more beneficial than those strategies aimed at changing the situation. This points to possible avenues for

designing adjunctive psychological therapies.

Manuscripts relevant to this research are in preparation. One manuscript dealing with genetic counseling with attention to the reasons why about 25% of the members of these families decline participation in this DNA-based genetic counseling will be submitted to the New England Journal of Medicine, as it contains important public health implications. A second manuscript dealing with the psychological evaluation of the genetic counseling interviews on more than 100 BRCA1 positive and negative patients is also in preparation.

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APPENDIX

Pedigrees of eight HBOC families where BRCA1 mutations have been identified.

I



Male 1 28 Lu53 55 354

Female 2 33 Br45 47 d86

Cancer by Pathology,
age at diagnosis
Current age

In-Situ Carcinoma by Pathology Report
Multiple Primary Cancers Unverified
Multiple Primary Cancers by
Medical Records or Death Certificates
Multiple Primary Cancers by Pathology
Cancer by Death Certificate or
Medical Records
Number of Unaffected Progeny
(Both Sexes)

Proband

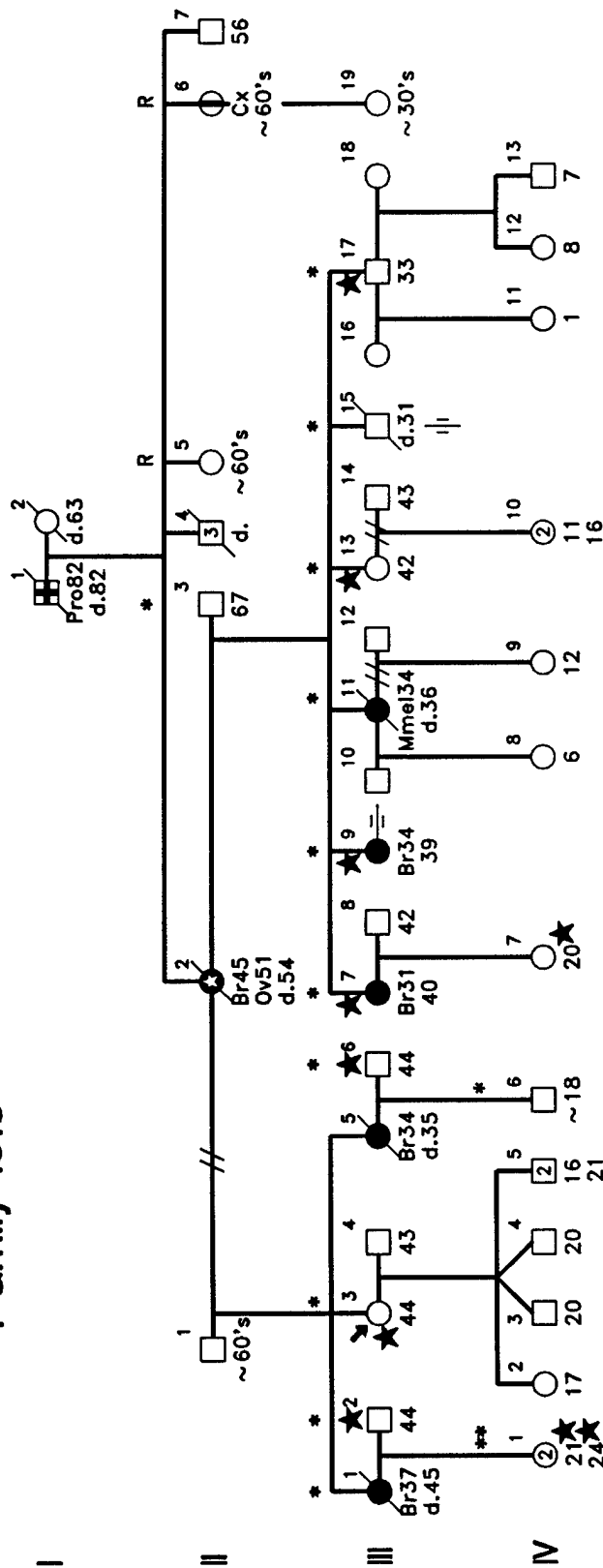
Br	Breast
Csu	Cancer Site Unknown
Cx	Cervix
Ki	Kidney
Mmel	Malignant Melanoma
Ov	Ovarian
Pan	Pancreas
Pro	Prostate
Sk	Skin

* Blood Sampled
★ Counseled in 1995

01/13/1995
2090-2

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Family 1813



LEGEND

Male
1
28

Female
2
33

Individual number
Unaffected
Current age

Cancer by Pathology,
age at diagnosis
Current age

Cancer by Family History,
age at death

Multiple Primary Cancers Unverified

Multiple Primary Cancers by
Medical Records or Death Certificates

Multiple Primary Cancers by Pathology

Cancer by Death Certificate or
Medical Records

Number of Unaffected Progeny
(Both Sexes)

Proband

Twins

Identical Twins

* Blood Sampled

R Refusing

★ Counselor in 1995

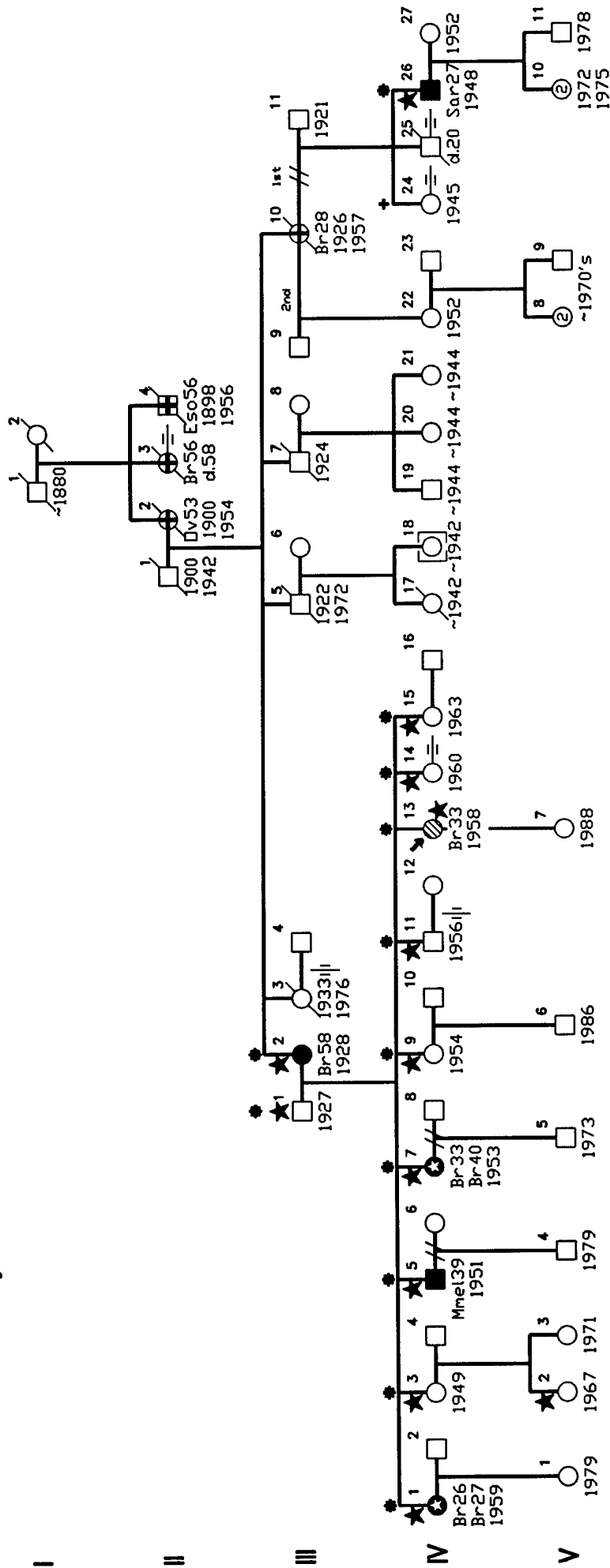
Cancer Sites

Br Breast
Cx Cervix
Ov Ovarian
Pro Prostate

01/19/1995
1813-2

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Family 1973



LEGEND

Male	Female	Individual number	Cancer Sites
1	2	Unaffected	
28	33	Current age	
35	47	Cancer by Pathology, age at diagnosis	Br Breast
35	47	Current age	Eso Esophagus
			Mmel Malignant Melanoma
			Ov Ovary
			Sar Sarcoma
		In-Situ Carcinoma by Pathology Report	
		Cancer by Family History, age at death	★ Blood Sampled
			+ Blood Kit sent
		Multiple Primary Cancers by Pathology	★ Counselor in 1995
		Cancer by Death Certificate or Medical Records	
		Number of Unaffected Progeny (Both Sexes)	
		Proband	

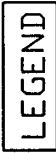
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03/29/1995
1973GR-2

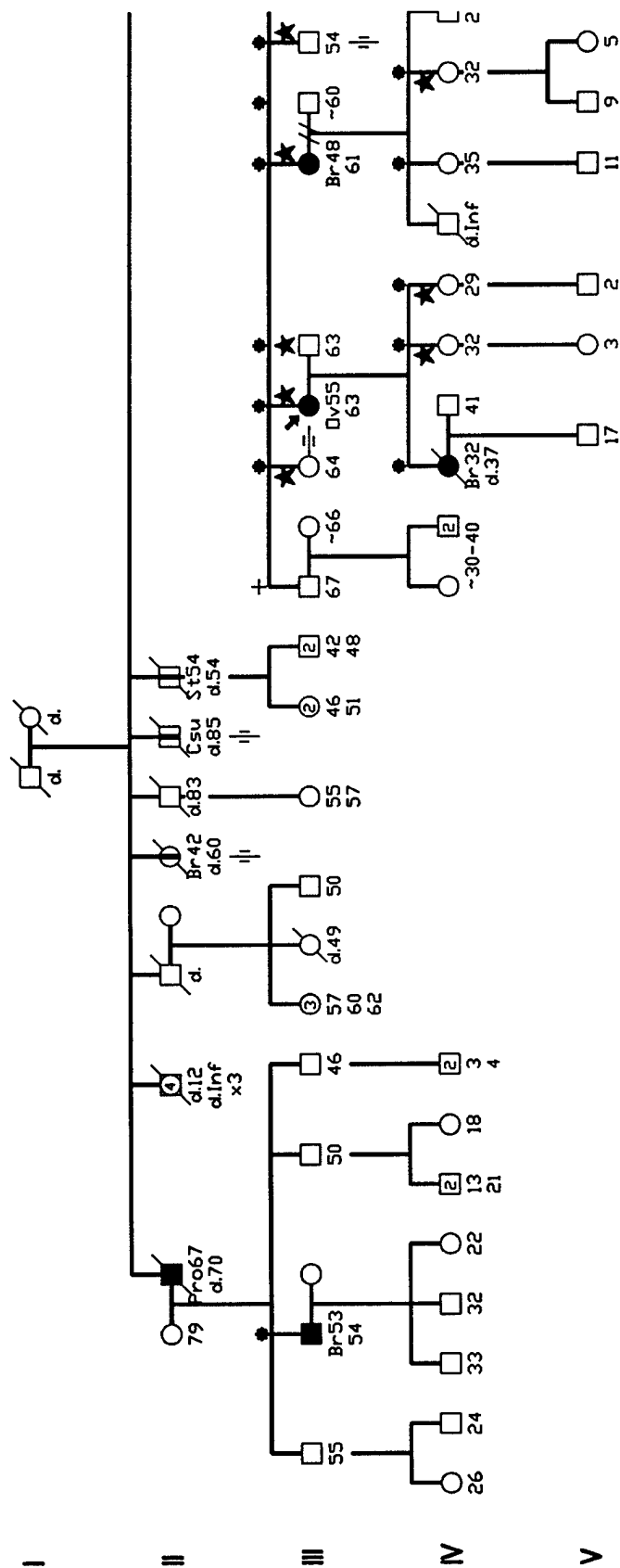
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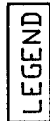


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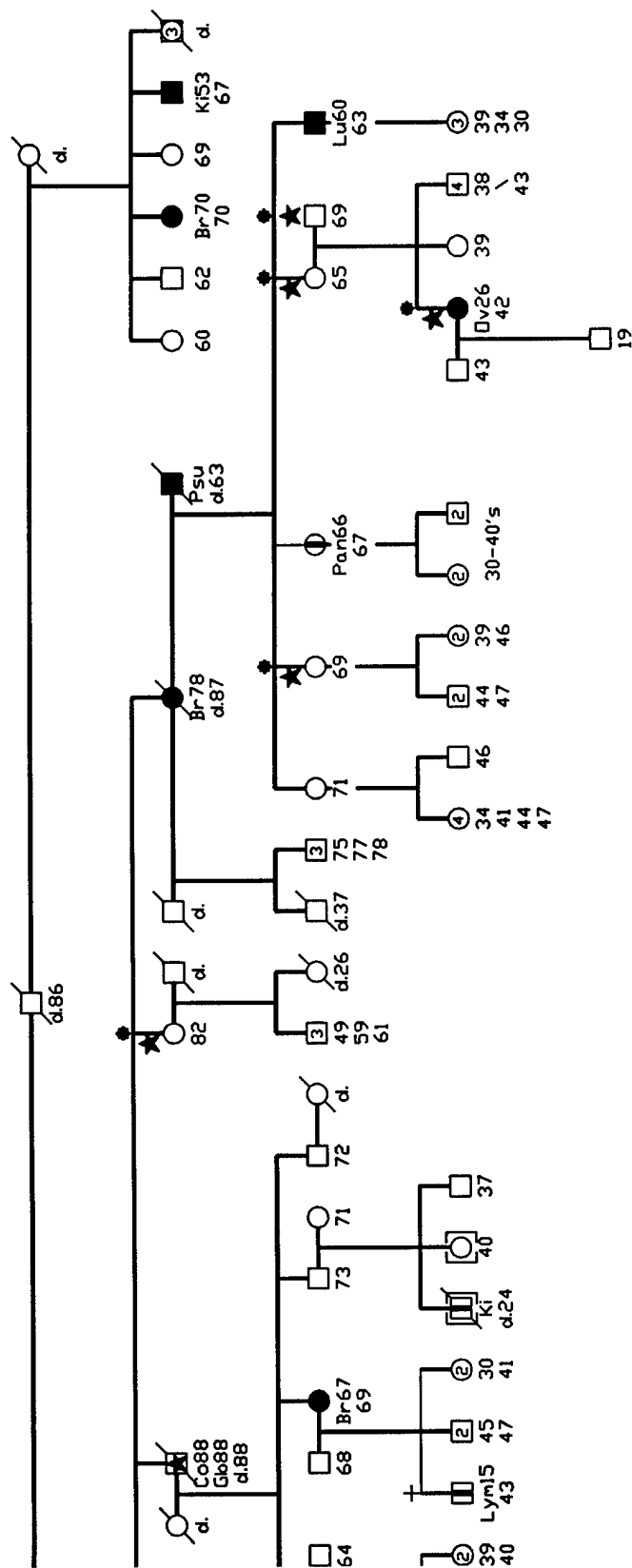


Identical Twins

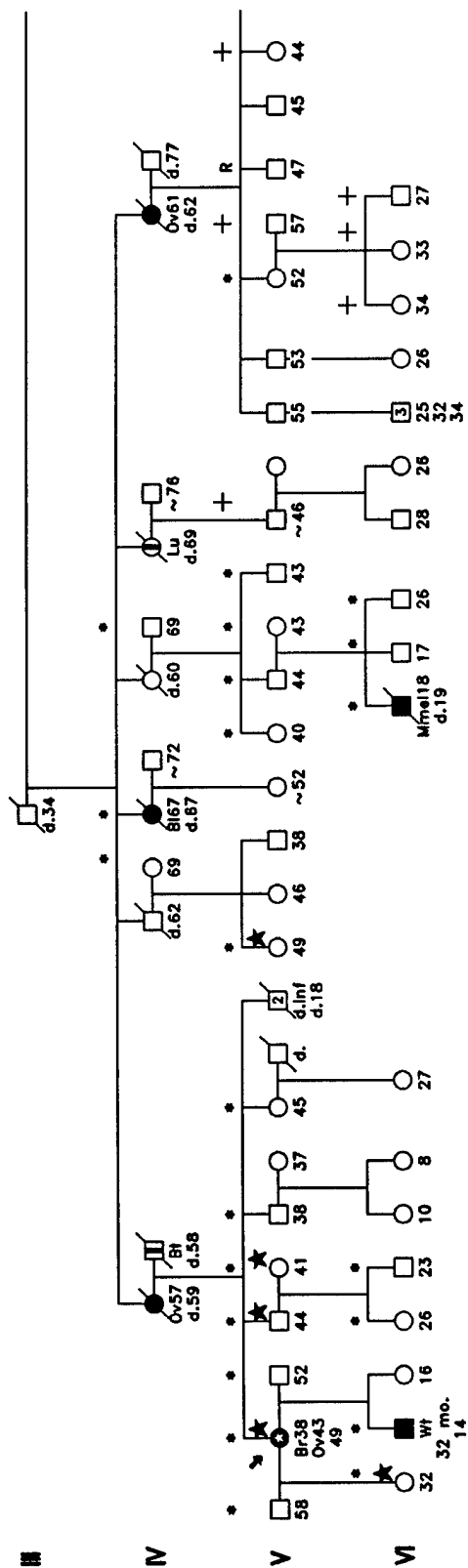
Blood Kit sent

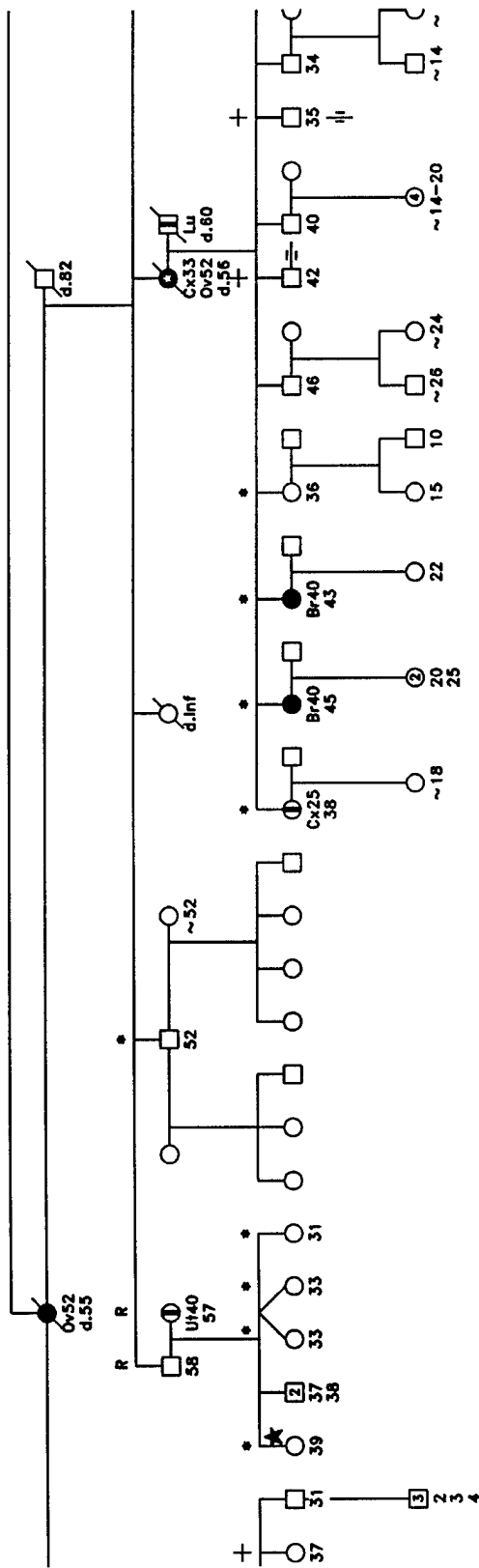
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I II III IV V VI





LEGEND

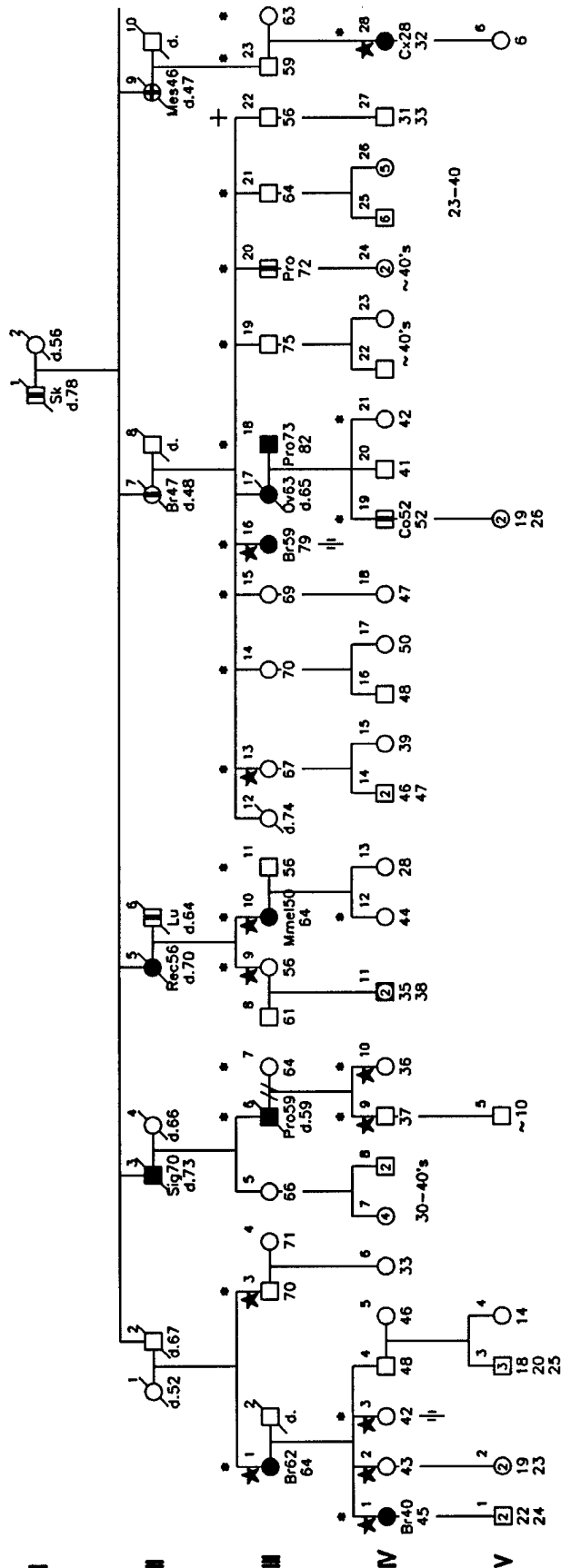
Cancer Sites				
Br	Breast			
Bl	Brain Tumor			
Cx	Cervix	+	Blood Kit sent	
Fe	Female			
Lg80	Large Bowel	*	Blood Sampled	
Lu	Lung	R	Refusing	
Mmel	Malignant Melanoma			
Mou	Mouth			
Ov	Ovarian			
Pan	Pancreas			
		★	Counseled In 1995	

98/15/1994
92319EL2

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Family 2770

Page 1 of 2



LEGEND

- Individual number
- Unaffected
- Current age
- Cancer by Pathology, age at diagnosis
- Cancer by Pathology, Current age
- In-Situ Carcinoma by Pathology Report
- Cancer by Family History, age at death
- Multiple Primary Cancers Unverified
- Multiple Primary Cancers by Medical Records or Death Certificates
- Multiple Primary Cancers by Pathology
- Cancer by Death Certificate or Medical Records
- Number of Unaffected Progeny (Both Sexes)
- Proband

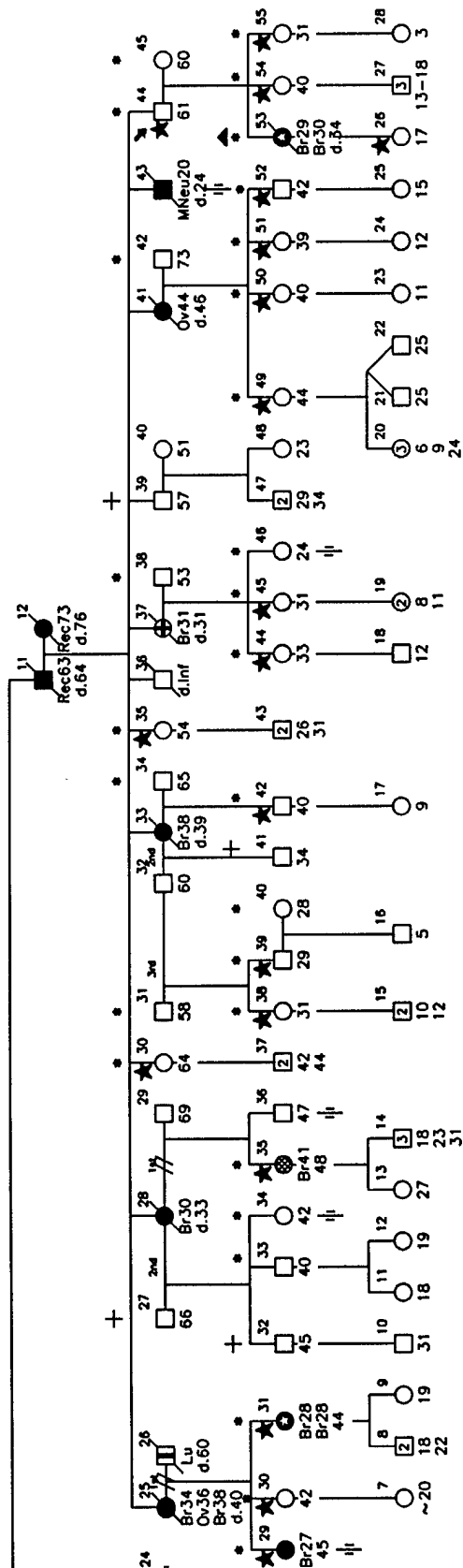
- Cancer Sites
- Br Breast
- Co Colon
- Lu Lung
- Mes Mesentery
- Mmel Malignant Melanoma
- MNeu Malignant Neurilemoma
- Ov Ovarian
- Pro Prostate
- Rec Rectal Colon
- Sig Sigmoid Colon
- Sk Skin

- ★ Counselor in 1995
- ▲ Tumor Tissue
- Blood Sampled
- + Blood Kit sent

03/15/1995
2770-7

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Family 1816

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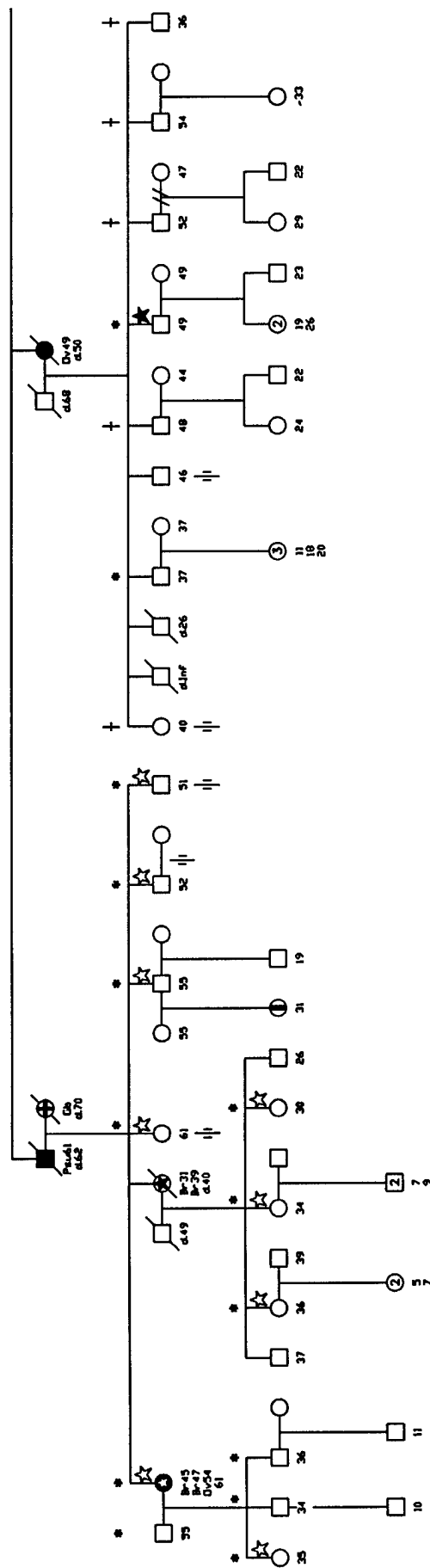
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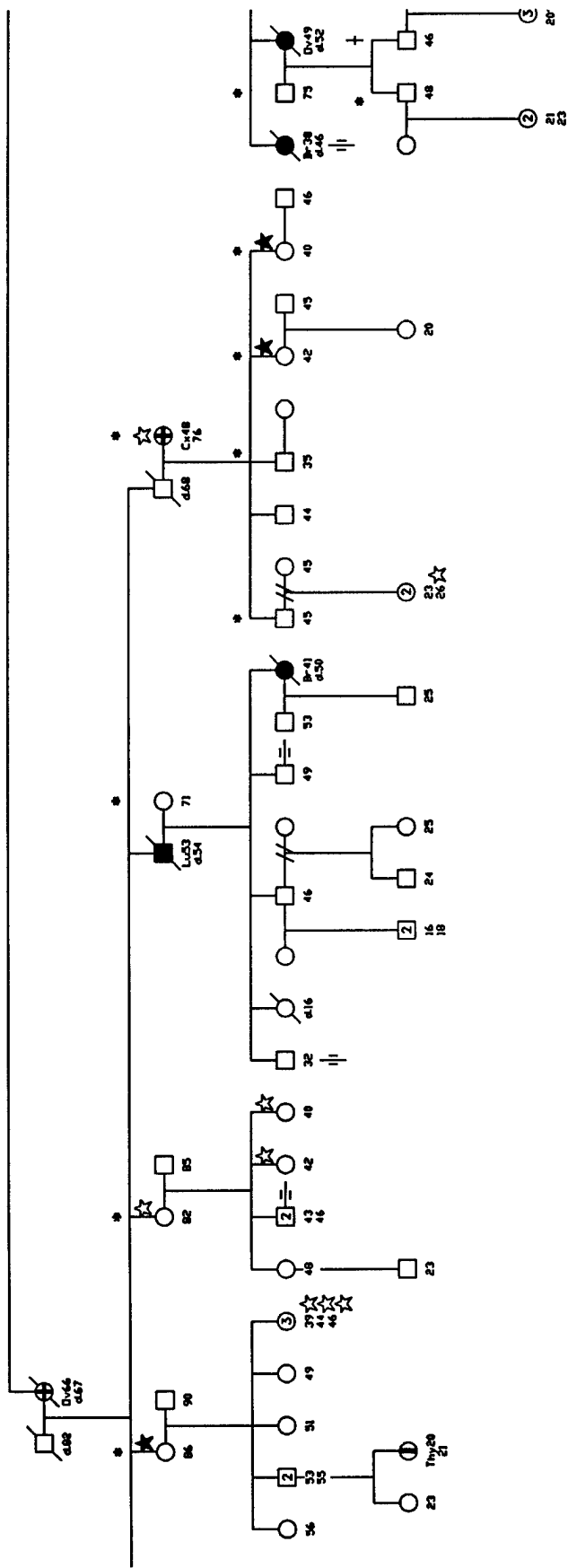
III

IV

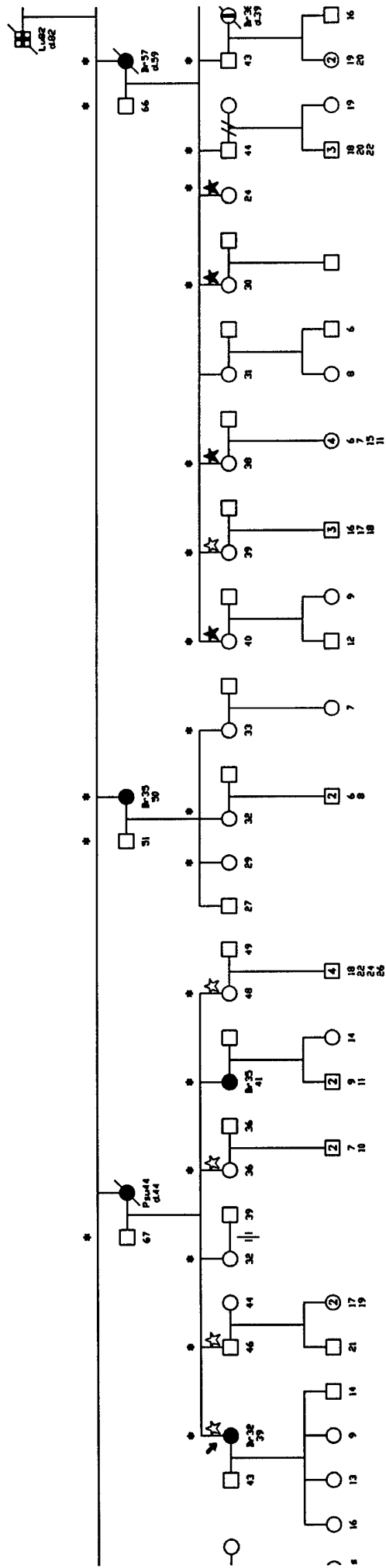
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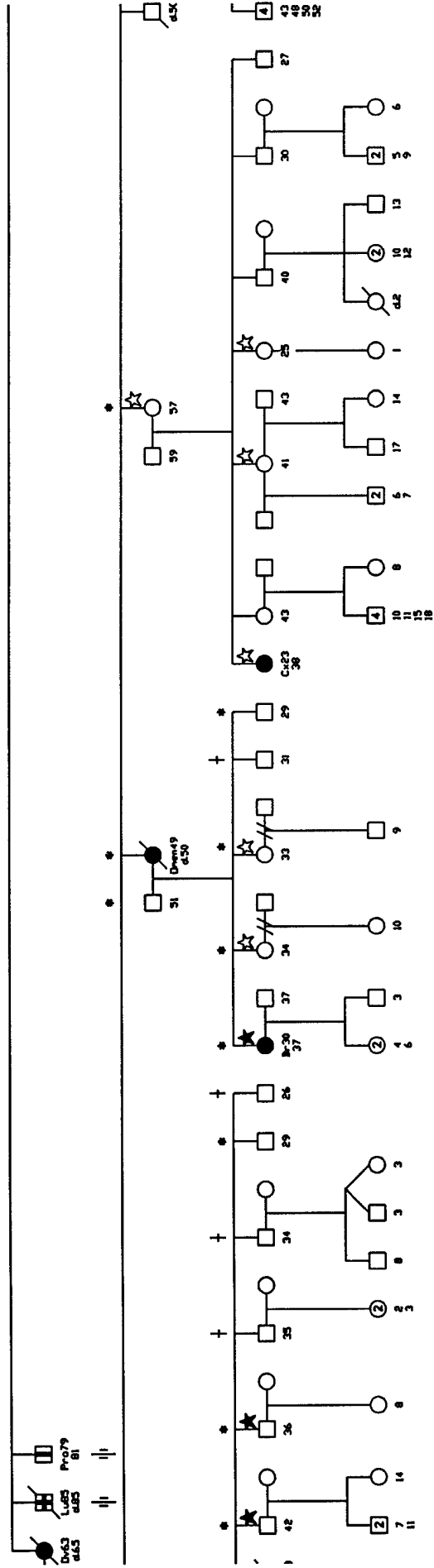
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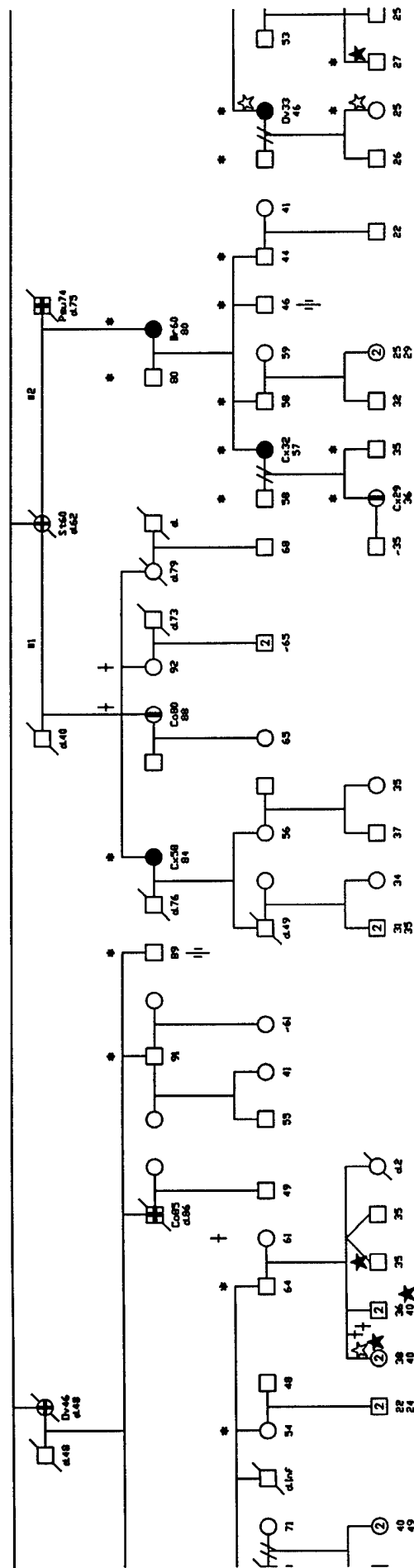




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LEGEND

- | | | |
|--|--|--|
| <p>Male</p> <p>Female</p> <p>Individual number</p> <p>Unaffected</p> <p>Current age</p> <p>Cancer by Pathology, age at diagnosis</p> <p>Current age</p> <p>Cancer by Family History, age at death</p> <p>Multiple Primary Cancers Unverified</p> <p>Multiple Primary Cancers by Medical Records or Death Certificates</p> <p>Multiple Primary Cancers by Pathology</p> <p>Cancer by Death Certificate or Medical Records</p> <p>Number of Unaffected Progeny (Both Sexes)</p> <p>Proband</p> <p>Twins</p> <p>Identical Twins</p> | <p>Bladder</p> <p>Breast</p> <p>Colon</p> <p>Cancer Site Unknown</p> <p>Cervix</p> <p>Gallbladder</p> <p>Leukemia</p> <p>Lung</p> <p>Malignant Melanoma</p> <p>Omentum</p> <p>Ovary</p> <p>Primary Site Unknown</p> <p>Stomach</p> | <p>* Blood Sampled</p> <p>+ Blood Kit sent</p> <p>☆ Counselled in 1992</p> <p>★ Counselled in 1995</p> |
|--|--|--|

Family 1816

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